Exhibit 6

medical essay
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OSTEOPOROSIS—The silent epidemic in women

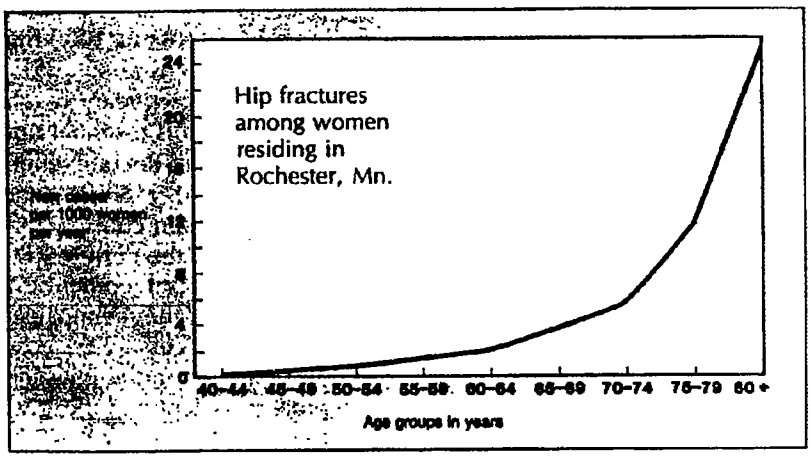
Osteoporosis is a major predisposing cause of bone fracture and an important health problem in women after age 50. Its economic impact is enormous. In the United States the yearly direct and indirect costs of osteoporosis and osteoporosis-related hip fractures exceed $3.8 billion. The frequent need for prolonged nursing home care following hip fracture may actually be the greatest long-term expense.

In spite of appropriate treatment of hip fractures, rehabilitation is often unsuccessful among elderly people. At least half of those ambulatory before a hip fracture cannot walk again after it occurs. Thus, the ability of such persons to get about and care for themselves is considerably limited and their quality of life seriously impaired. One out of eight elderly persons who suffer a hip fracture will die of complications within the first four months.

In addition to hip fractures, breaks in the wrist bones and compression ("crush") fractures of the spinal vertebrae add greatly to the toll of pain and disability and to the economic burden of this condition. It has been estimated that 1 million fractures of the hip, wrist and spine each year in the United States are caused by osteoporosis.

What is osteoporosis?

Osteo = bone and porosis = increased pores. The interior structure of many bones normally resembles a sponge. Osteoporotic bone is like a sponge in which the holes are enlarged with resulting weakness and fragility (see illustration). In osteoporosis progressive thinning of the bones may leave the skeleton too fragile to withstand even minimal mechanical stress. The bones gradually weaken and become prone to fractures.



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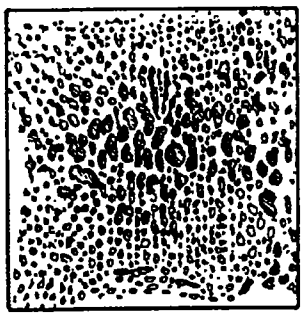
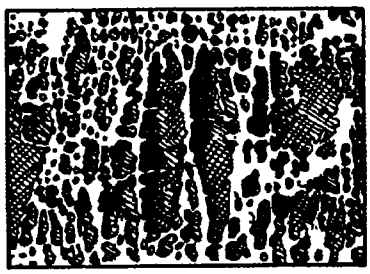


Normal bone



Osteoporotic bone

Who is at greatest risk for osteoporosis?

Women after the menopause are by far the largest group of people who develop osteoporosis that leads to fractures. Elderly men also may have osteoporosis but less commonly and less severely than women. Caucasians are affected much more frequently than Blacks. Cigarette smoking and alcohol consumption also appear to be risk factors, but the reasons for this are not well understood.

Slender women who exercise little are more likely to develop the condition than those of heavier build who are more physically active. Prolonged inactivity, especially bed rest, is also a predisposing factor (see *Mayo Clinic Health Letter,* November 1983).

What causes osteoporosis?

The loss of bone mineral may arise from a great variety of causes. The major factor in postmenopausal women is deficiency of estrogen—the main female sex hormone. Removal of the ovaries from young women results in a prompt drain of calcium from the skeleton. At the time of the naturally occurring menopause, a similiar loss of bone mineral occurs. This decrease is considerably greater than in men of similar age.

Normal bone undergoes continuous remodeling, as do most body tissues. The amount of mineralized bone at any time is a balance between these breakdown and rebuilding processes. In those with osteoporosis, the rate of bone loss ("resorption") exceeds the rate of new bone formation ("accretion"). Estrogen deficiency is a major factor in causing this negative balance.

What role does calcium play in osteoporosis?

Since the mineral content of bone is continually being renewed, insufficient amounts of calcium in the diet play a major role in development of osteoporosis. In the United States, dairy products are the major dietary sources of calcium. Milk, cheese, yogurt and buttermilk are all good sources of calcium. One quart of whole or skim milk contains 1000 mg of calcium. A one-ounce slice of Swiss cheese contains about 270 mg. Sardines are also a good source of calcium. Green, leafy vegetables such as broccoli contain modest amounts of this essential nutrient, but it is not well absorbed.

1000 mg / 32 fl. oz =
31.25 mg / fl. oz =
137.5 / 4 fl. oz =
250 mg / 8 fl. oz.

The adult Recommended Daily Allowance (RDA) for calcium is 800 mg per day. Surveys indicate that the diets of many adult women contain considerably less than this amount. Some authorities now believe the current RDA is too low, especially in postmenopausal women. They suggest up to 1500 mg per day for women after the menopause. A higher intake for postmenopausal women is necessary because estrogen deficiency may impair calcium absorption from the intestine. Those whose diet has a relatively high protein content and those who eat a diet high in fiber also may require extra dietary calcium.

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Calcium has been called the forgotten nutrient of Western society. Many people stop drinking milk and reduce intake of other calcium-rich dairy products after adolescence. Lifelong dietary habits (typically characterized by a low calcium intake) are difficult to change. Some people who don't like the taste of milk may be able to increase consumption by disguising it in ice cream, hot cereal, puddings, omelets, baked goods and casseroles. However, some individuals have difficulty digesting milk sugar (lactose) so that ingestion of milk and milk-containing foods causes intestinal gas and diarrhea (see *Mayo Clinic Health Letter,* March 1984). If it is not feasible to increase dietary intake of calcium, it may be necessary to take special calcium supplements.

Some physicians believe that ensuring adequate calcium content earlier in life might increase bone density. Thus, even though a reduction in bone mineral content develops later in life, the bones might still be strong enough to prevent some of the fractures now suffered by older women with osteoporosis. Some studies suggest that a high calcium intake over a period of years might retard bone loss enough to reduce susceptibility to fractures.

What are the symptoms of osteoporosis?

There are no early warnings. The diagnosis is frequently not made until after a disabling bone fracture. Due to progressive

FOODS HIGH IN CALCIUM

Food	Serving size	Calcium content (mg)
Collard (cooked)	1 cup	357
Kale (cooked)	1 cup	179
Milk	8 oz	285
Cheese		
American	1 oz	174
Cheddar	1 oz	204
Low-fat cottage	8 oz	138
Swiss	1 oz	272
Ice cream	8 oz	176
Milk	8 oz	300
Salmon (canned)	3 oz	285
Sardines (with bones)	3 oz	372
Shrimp	8 oz	147
Turnip greens (cooked)	8 oz	267
Yogurt		
Low-fat plain	8 oz	415
Low-fat fruited	8 oz	314
Frozen	8 oz	200

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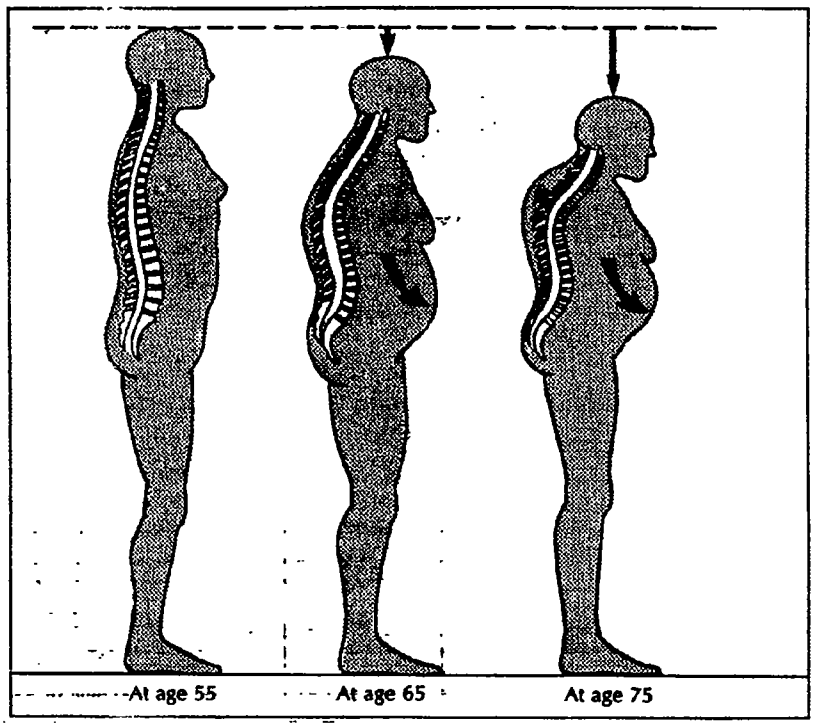
vertebral compression, women often note a gradual loss of height, starting after the menopause. This is frequently accompanied by forward bending of the upper spine (doctors call this dorsal kyphosis) with a protuberance known as "dowager's hump." The compression fractures of the vertebrae commonly cause pain in the back.

The loss of height also results in a prominence of the abdomen—"pot belly." This frequently is puzzling to women, since their weight does not increase and there are usually no other areas of apparent obesity in the body.

How is the diagnosis made?

Your physician will do appropriate studies to be sure there is not another medical condition present which may mimic postmenopausal osteoporosis.

As noted earlier, the diagnosis may not be suspected until a fracture prompts a person to seek medical attention. Ordinary x-ray films do not reveal osteoporosis until marked loss of bone mineral has already occurred. Sophisticated instruments to measure bone density and specialized chemical determinations of blood and urine are available in research centers to detect the early development of osteoporosis. These tests are expensive and are not yet available for screening the vast majority of older women. Thus, all women after



Progressive vertebral compression, caused by osteoporosis, results in a gradual loss of height in women and often is accompanied by a forward bending of the upper spine which leads to a condition known as "dowager's hump." Insufficient amounts of calcium in the diet and deficiency of estrogen play major roles in development of osteoporosis.

the menopause should be regarded as being potentially at risk for this condition. Careful measurement of your height each year is one of the simplest ways to detect osteoporosis affecting the spine.

How is osteoporosis treated?

Preventive treatment is best. An adequate dietary calcium intake throughout life, with extra calcium supplements if necessary, is important. Regular physical exercise is one of the best ways for women to help maintain strong bones. Women whose ovaries must be surgically removed early in life usually are given estrogen to prevent premature menopause symptoms.

Until recently, many physicians were reluctant to prescribe estrogen over prolonged periods for women after the normal menopause. There is an increased risk of developing cancer of the lining of the uterus (endometrium) from prolonged estrogen use. This hazard must be balanced against the pain and disability of wrist and spine fractures and the risk of death following hip fracture in women who develop osteoporosis as a result of estrogen deficiency. Use of progesterone tablets (another female sex hormone) during part of the monthly cyclic administration of estrogen may reduce the risk of cancer. Your personal physician should discuss these matters with you before a decision is reached about prolonged treatment with hormones.

For those with osteoporosis affecting the vertebrae, improving muscular support of the spine by proper strengthening exercises may be helpful. This exercise program may not be possible in those with painful crush fractures and should be prescribed individually. A firm mattress with a plywood board underneath improves spinal support during sleep. A thin pillow against the back of the chair gives support to the lower back while sitting. A properly fitting back support with shoulder straps often relieves back pain and improves posture. Avoiding heavy lifting and bending activities helps to prevent further vertebral damage.

Is fluoride treatment helpful?

Fluoride (in the form of sodium fluoride tablets) treatment for osteoporosis is under long-term study at Mayo Clinic and other medical centers. It is still regarded as experimental and is not yet approved by the U.S. Food and Drug Administration for general use in the treatment of this disorder.

The use of calcium supplements and estrogen may help stop continuing loss of bone but does not replace bone mineral already gone. Fluoride stimulates new bone growth and has the potential to reverse the process. The effect of fluoride on increasing bone density was initially noted in people whose drinking water contained high amounts of fluoride.

Unfortunately, fluoride treatment also may have troublesome side effects, including stomach upset and rheumatic symptoms in the legs and feet. These problems are relieved when fluoride is stopped. Researchers are trying to find a dose level which will be effective in strengthening bone without causing the undesirable effects.

What about future developments?

Studies of the most effective treatment of *established* osteoporosis are under way. The combined use of estrogen, supplementary calcium and fluoride looks promising. Treatment with these three agents can't be expected to improve bone strength rapidly, but studies show that by the second year of use the risk of bone fractures is considerably reduced.

In the long run, *prevention* of this disorder is the most cost-effective approach. Research now in progress may define a group of postmenopausal women most susceptible to fractures due to osteoporosis. Identification of these individuals will allow a more concentrated effort to prevent the disease and its disabling complications.

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